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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/771,382	01/25/2001	Ian Richard Anselm Peak	8795-24 UI	6450

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2005 MARKET STREET, SUITE 2200
PHILADELPHIA, PA 19103

EXAMINER	
FORD, VANESSA L	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 01/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/771,382	PEAK ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33,34 and 49-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *33,34 and 49-52* is/are allowed.

6)☒ Claim(s) *53-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL ACTION

1. This Office Action is responsive to Applicant's amendment and response filed October 5, 2005. Claims 1-32 and 35-48 have been cancelled. Claims 49-58 have been added.

2. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

Rejections Withdrawn

3. In view of Applicant's amendment the following rejections are withdrawn.

a) Rejection of claims 38-39 and 44-48 under 35 U. S.C. 102(a), page 7-9, paragraph 3 of the previous Office action.

b) Rejection of claims 38-39 and 44-48 under 35 U. S.C. 102(a), page 9-11, paragraph 4 of the previous Office action.

c) Rejection of claims 38-39 and 44-48 under 35 U. S.C. 102(e), page 11-13, paragraph 5 of the previous Office action.

Rejection Maintained

4. The rejection under 35 U.S.C. 112, first paragraph (enablement) is maintained for newly submitted claims 53-58 for the reasons set forth on pages 2-7, paragraph 2 of the previous Office Action.

The rejection was on the grounds that the claims (newly submitted claims 53-58) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated proteins as set forth in SEQ ID NOs: 23 and 35 and compositions comprising the isolated proteins, does not reasonably provide enablement for proteins that are variants of SEQ ID NOs: 23 or 35 or compositions comprising these proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant specification broadly discloses a genus of polypeptides that comprises SEQ ID NO:23 and SEQ ID NO:35. The instant specification teaches that SEQ ID NO: 23 is the amino acid sequence of a PMC 21 NhhA deletion mutant polypeptide (page 8 and Example 4). The instant specification teaches that SEQ ID NO: 35 is the amino acid sequence of a predicted mature protein described in Example 4 (page 10 and Example 4). The instant specification teaches that recombinant DNA-based production of the polypeptides of the invention can be accomplished by the deletion of one or a few amino acids of the (conserved) C1, C2, C3, C4 and/or C5 or (variable) V1, V2, V3 and/or V4 regions of the consensus polypeptide (SEQ ID NO:11) (page 13). The specification teaches that SEQ ID NO:11 comprises constant regions of NhhA polypeptide designated as C1-C5 and non-conserved regions designated as V1-V-4 (page 3). The instant specification teaches that V1-V4 are non-conserved amino acids of a variable region (page 3). Therefore, the non-conserved regions of SEQ ID NO:11 can comprise any amino acid. Thus, the claimed polypeptide as set forth in SEQ ID NO:11 as well as variants of SEQ ID NOs. 23 and 35 can include any substitution or change of amino acids throughout regions V1-V4 of the polypeptide sequence. Therefore, SEQ ID No: 11 and variant or fragments of SEQ ID NOs: 23 and 35 can correspond to mutated sequences, allelic variants, splice variants, sequences that have a variant degree of identity (similarity, homology), and so forth are being claimed. There is no guidance provided as to which amino acids can be substituted, inserted or deleted and the polypeptide would retain its biological function. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence

and still retain similar activity/utility requires a knowledge with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the polypeptide's structure relates to function. However, the problem of the prediction of polypeptide structure from mere sequence data of a single polypeptide and in turn utilizing predicted structural determinations to ascertain functional aspects of the polypeptide and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation. There is no guidance as to what amino acids may not be changed without causing a detrimental effect to the polypeptide being claimed. The claims broadly teach polypeptides, which include substitutions and/or deletions, therefore any polypeptide is being claimed, and no specific location for the deletion, substitution or any combination thereof is recited. Thus, the resulting polypeptide could result in a polypeptide not taught nor enabled by the specification.

The claims of the instant application are not only drawn to a isolated proteins but are also drawn to isolated proteins that have at least 80% or at least 90% identity to SEQ ID NOs. 23 and 35. Thus, the claimed isolated proteins include variants as well as fragments of SEQ ID NOs 23 and 35. There is no guidance provided in the specification as how one would begin to choose " variants or fragments" of SEQ ID NOs: 23 or 35. The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does not disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of sequence(s) which can be predictably modified and which regions are critical;
- what fragments, if any, can be made which the retain the biological activity if the intact protein; and
- the specification provide essentially no guidance as to which of the essentially infinite possible choice is likely to be successful.

Thomas E. Creighton, in his book, "*Proteins: Structures and Molecular Properties, 1984*", (pages 314-315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a Praline residue, which must distort the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book "*Protein Structure: A Practical Approach, 1989; pages 184-186*" teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in "*Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph)* adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Therefore, the specification fails to provide guidance regarding how to make and use polypeptides that fall within the broadly claimed genus of SEQ ID NO:11 that retain the claimed activity as well as how to make and use variants or fragments of SEQ ID NOs: 23 and 35.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting polypeptides that fall within the broadly claimed genus of variants or fragments of SEQ ID NOs: 23 and 35 having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use polypeptides that are fall within the broadly claimed genus variants or fragments of SEQ ID NOs: 23 and 35 in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

Applicants Arguments:

A) Applicant urges that newly submitted claims 53 and 56 comply with the written description and enablement requirements under 35 U.S.C. 112, first paragraph. Applicant urges that claims 53 and 56 cover variants which possess a high degree of sequence similarity to SEQ ID NOs: 23 and 35 which possess the functional capability of eliciting an immune response to a plurality of strains of *N. meningitidis.*

B) Applicant urges that Fig.1 and Table I of the instant specification provides substantial guidance to the skilled person as to which amino acids may be deleted or modified and which amino acid residues should be retained in order to satisfy this functional requirement. Applicant urges that the Examples provide several recombinant strategies for constructing such isolated proteins. Applicant urges that for example, SEQ ID NO: 35 comprises entire V3, V4, C4 and C5 regions, with part of the C3 region of PMC21 (SEQ ID NO:1) and by substituting one or more of the corresponding regions of any of the other *N. meningitdiis* strain sequences as set forth in SEQ ID NO:2-10 for those of SEQ ID NO:35, the specification provides explicit support for variants of SE ID NOs: 23 and 35.

C) Applicant urges while the specification did not literally recite each of these variants sequences by sequence, Applicants submit that this type of laborious *ipsis verbis* recitation is not required to provide proper written description.

Examiner's Response to Applicant's Arguments:

A) It is the Examiner's position that claims 53-58 do not comply with 35 U.S.C. 112, first paragraph. Applicant has shown how to make and use SEQ ID Nos: 23 and 35 but has not shown how to make variants of the polypeptide as set forth in SEQ ID Nos:23 and 35 that retain the same functional properties. It should be remembered that the statute under 35 U.S.C. 112, first paragraph requires that Applicant teach how to make and use the claimed invention and not how to find variants of SEQ ID NO:23 and SEQ ID NO:35. One of skill in the art would not conclude that Applicant has enabled polypeptides that are variants of SEQ ID NOs: 23 and 35 based on what is enclosed in the instant specification.

To address Applicant's comments regarding written description, it should be remembered that the rejection of record is an enablement rejection.

Applicant has not meet the burden required under 35 U.S.C. 112, first paragraph.

B) To address Applicant comments regarding Figure 1 and Table I of the instant specification, the figure and table merely disclose the conserved regions and variable regions which are used to generate a consensus sequence from 10 strains of *N. meningitidis* strains. Figure 1 and Table 1 in no way convey which amino acids are modified along the amino acid sequence as set forth in SEQ ID NO:23 or SEQ ID NO:35 nor do Figure 1 or Table 1 convey what positions are modified along the amino

acid sequence as set forth in SEQ ID NO:23 or SEQ ID NO:35 to arrive at variant polypeptides that have the same or similarly functional properties as the polypeptides set forth in SEQ ID NOs:23 and 35. Applicant has not provided structure for the claimed genus of polypeptides encompassed by the claimed invention.

C) While Applicant is not required to literally recite each variant that is encompassed by the claims, however, Applicant is required to show how to make and used the claimed polypeptides. Therefore, to satisfy the requirement under 35 U.S.C. Applicant is required to disclosed a structure for a representative number of species within the claimed genus of polypeptides.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 53-58 are rejected under 35 U.S.C. 102(a) as anticipated by Masignani et al *(WO 99/36544 published July 22, 1999)*.

Claims 53-58 are drawn to an isolated protein, the entire amino acid sequence of which has at least 80% sequence identity to the entire amino acid sequence set forth in SEQ ID NO:35 wherein the isolated protein is capable of eliciting an immune response to a plurality of strains of *N. meningitdis* and an isolated protein, the entire amino acid sequence of which has at least 90% sequence identity to the entire amino acid sequence set forth in SEQ ID NO:23 or SEQ ID NO:35 wherein the isolated protein is capable of eliciting an immune response to a plurality of strains of *N. meningitdis*.

Masignani et al teach proteins from *Neisseria meningitidis* and immunogenic compositions as well as pharmaceutical compositions containing the polypeptide (see the Abstract and pages 29-30). Masignani et al teach a protein (SEQ ID NO:4)(page 62) that has over 98% identity to SEQ ID NO: 23. Masignani et al teach a protein (SEQ ID NO:4) (page 62) that has over 99% identity to SEQ ID NO: 35.The protein and pharmaceutical compositions of Masignani et al appear to be the same as the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's protein and pharmaceutical compositions with the protein and pharmaceutical compositions of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein and pharmaceutical compositions of the prior art does not possess the same material structural and functional characteristics of the claimed

protein and pharmaceutical compositions). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

6. Claims 53-58 are rejected under 35 U.S.C. 102(a) as anticipated by Peak et al *(WO 99/31132 published June 24, 1999).*

Claims 53-58 are drawn to an isolated protein, the entire amino acid sequence of which has at least 80% sequence identity to the entire amino acid sequence set forth in SEQ ID NO:35 wherein the isolated protein is capable of eliciting an immune response to a plurality of strains of *N. meningitdis* and an isolated protein, the entire amino acid sequence of which has at least 90% sequence identity to the entire amino acid sequence set forth in SEQ ID NO:23 or SEQ ID NO:35 wherein the isolated protein is capable of eliciting an immune response to a plurality of strains of *N. meningitdis.*

Peak et al teach proteins from *Neisseria meningitidis* and pharmaceutical compositions containing the polypeptide (see the Abstract and pages 34-40). Peak et al teach a protein (SEQ ID NO:2)(page iv –v of sequence listing) that has over 98% identity to SEQ ID NO: 23. Peak et al teach a protein (SEQ ID NO:2) (page iv-v of sequence listing) that has over 99% identity to SEQ ID NO: 35.The protein and pharmaceutical compositions of Peak et al appear to be the same as the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's protein and pharmaceutical compositions with the protein and pharmaceutical compositions of the prior art, the burden is on the applicant to show a

novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein and pharmaceutical compositions of the prior art does not possess the same material structural and functional characteristics of the claimed protein and pharmaceutical compositions). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

7. Claims 53-58 are rejected under 35 U.S.C. 102(e) as anticipated by Peak et al *(U. S. Patent No.6,197,312 B1 published March 2001).*

Claims 53-58 are drawn to an isolated protein, the entire amino acid sequence of which has at least 80% sequence identity to the entire amino acid sequence set forth in SEQ ID NO:35 wherein the isolated protein is capable of eliciting an immune response to a plurality of strains of *N. meningitdis* and an isolated protein, the entire amino acid sequence of which has at least 90% sequence identity to the entire amino acid sequence set forth in SEQ ID NO:23 or SEQ ID NO:35 wherein the isolated protein is capable of eliciting an immune response to a plurality of strains of *N. meningitdis.*

Peak et al teach proteins from *Neisseria meningitidis* and pharmaceutical compositions containing the polypeptide (see the Abstract and pages 34-40). Peak et al teach a protein (SEQ ID NO:2)(columns 31-33) that has over 98% identity to SEQ ID NO: 23. Peak et al teach a protein (SEQ ID NO:2) (columns 31-33) that has over 99% identity to SEQ ID NO: 35.The protein and pharmaceutical compositions of Peak et al appear to be the same as the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's protein and pharmaceutical compositions with the protein and pharmaceutical compositions of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein and pharmaceutical compositions of the prior art does not possess the same material structural and functional characteristics of the claimed protein and pharmaceutical compositions). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Status of Claims

8. Claims 33-34 and 49-52 appear to be free of the cited prior art.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

10. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
January 3, 2006

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